

What is claimed is:

1. A method for identifying a subject at risk of low BMD, which comprises detecting the presence or absence of one or more polymorphic variations associated with low BMD in a nucleic acid sample from a subject, wherein the one or more polymorphic variations are detected in a nucleotide sequence in SEQ ID NOs:1-5, a substantially identical sequence thereof or a fragment of the foregoing; whereby the presence of the polymorphic variation is indicative of the subject being at risk of low BMD.

2. The method of claim 1, which further comprises obtaining the nucleic acid sample from the subject.

3. The method of claim 1, wherein the one or more polymorphic variations are detected at one or more positions selected from the group consisting of rs7500979, rs2217332, rs8044804, rs2270835, rs2133783, rs247609, rs952440, rs881598, rs2291955, rs2518054, rs866038, rs1436425, rs173537, rs247611, rs166017, rs173538, rs193694, rs7205692, rs8048746, rs247618, rs183130, rs6499863, rs4783961, rs3816117, rs711752, rs708272, rs1864163, rs4369653, rs1864165, rs891141, rs891143, rs7205804, rs5885, rs1532625, rs1532624, rs289712, rs7499892, rs5883, rs289714, rs158480, rs289717, rs4344729, rs289718, rs289719, rs2033254, rs4784744, rs291044, rs8053613, rs5881, rs5880, rs7198026, rs5882, rs8045701, rs289741, rs1801706, rs289742, rs289743, rs289746, rs172337, rs289747, rs1566439, rs7205459, rs289749, rs289751, rs8059220, rs8058353, rs289735, rs289737, rs291042, rs1875236, rs821466, rs821465, rs4275846, rs289707, rs821463, rs289706, rs1167741, rs2052880, rs1167742, rs1183256, rs1651665, rs1651666, rs4784751, rs1651667, rs8052091, rs1684574, rs1684575, rs1672865, rs821470, rs1549669, rs291040 and rs289754.

4. The method of claim 1, wherein the one or more polymorphic variations are detected at one or more positions selected from the group consisting of rs166017, rs193694, rs7205804, rs1801706, rs7205459 and rs821465.

5. The method of claim 1, wherein the one or more polymorphic variations are detected in a region spanning positions 14,328 to 68,805 in SEQ ID NO: 1.

6. The method of claim 1, wherein the one or more polymorphic variations are detected at one or more positions selected from the group consisting of rs523051, rs693620, rs2588349, rs2588350, rs619381, rs3759252, rs3759251, rs2418107, rs7303054, rs1838345, rs620878, rs2537817, rs1548803, rs667123, rs1838346, rs2159903, rs3944035, rs3741845, rs2110096, rs759055, rs589377, rs7960194, rs7978242, rs601051, rs4262797, rs2215714, rs1373434, rs2215715, rs612456, rs612808, rs689118, rs597468, rs592864, rs640372, rs7966559, rs654834, rs4763216, rs668521, rs669503,

rs3906864, rs3906863, rs7957888, rs9300230, rs7306214, rs763839, rs2418105, rs666841, rs3851578, rs7138797, rs7295252, rs2418106, rs7299578, rs621112, rs3863320, rs1373432, rs1047699, rs1063193, rs2232959, rs2227296, rs1548804, rs2232958, rs2232957, rs2232956, rs1972571, rs3759250, rs3759249, rs1541525, rs2098248, rs2900550, rs7302130, rs4763583, rs4360778, rs1607695, rs1607694, rs2192139, rs7978300, rs7397871, rs4763217, rs2159900, rs10772370, rs7398682, rs2900551, rs2900552, rs2418214, rs2418215, rs965243, rs1117548, rs1520225, rs1520226, rs1520227, rs971919, rs2159901, rs2159902, rs2110099, rs7314847, rs7296003, rs4281556, rs4763219, rs3851579, rs3851580, rs1049119, rs2298866, rs2298865, rs2298864, rs2298863, rs3180393, rs2070837, rs7956204, rs2418216, rs3741844, rs4262798, rs2418217, rs2418218, rs7137492, rs2110100, rs1013312, rs4579993, rs1013313, rs7397106, rs2215716, rs2192140, rs4763589, rs1468697, rs2070837, rs3180393 and rs2298865.

7. The method of claim 1, wherein the one or more polymorphic variations are detected at one or more positions selected from the group consisting of rs2588350, rs619381, rs620878, rs759055, rs4262797, rs612808, rs3906863, rs7957888, rs763839, rs2418105, rs666841, rs3851578, rs7299578, rs621112, rs1047699, rs1548804, rs2232956, rs1520227 and rs2215716.

8. The method of claim 1, wherein the one or more polymorphic variations are detected in a region spanning positions 2,424 to 93,715 in SEQ ID NO: 2.

9. The method of claim 1, wherein the one or more polymorphic variations are detected at one or more positions selected from the group consisting of rs1433661, rs1485009, rs7681947, rs1816432, rs1485018, rs1485017, rs7438397, rs6834311, rs1368717, rs1017391, rs2870701, rs7679839, rs1385404, rs1368716, rs4693316, rs1905707, rs1905708, rs1905709, rs3912442, rs2082553, rs6831638, rs5860329, rs2870702, rs2870703, rs1948016, rs6835836, rs1994253, rs1905710, rs1485019, rs978191, rs1385405, rs7694361, rs1905711, rs1905734, rs1485012, rs1485013, rs4692981, rs7670552, rs7670932, rs7688091, rs7440540, rs2171000, rs2870704, rs7655758, rs7661436, rs7662289, rs7667044, rs7691929, rs5860330, rs901013, rs901012, rs901011, rs1948018, rs2870705, rs1948017, rs1905733, rs1385408, rs1385409, rs1385410, rs1485026, rs1485027, rs2904483, rs1385406, rs1905732, rs2046418, rs2200377, rs1905731, rs1905730, rs975713, rs6820985, rs7670441, rs6810794, rs7676623, rs1154861, rs1032125, rs1485022, rs1485024, rs3913651, rs4693319, rs1872383, rs2200376, rs7668090, rs7692930, rs967096, rs6822249, rs6532405, rs1017897, rs7672674, rs7694568, rs2904484, rs7340830, rs1485033, rs2870706, rs1905729, rs4693320, rs6848749, rs6532406, rs6532407, rs1905728, rs6819866, rs1905727, rs7674069, rs1905724, rs1905723, rs1485020 and rs6814101.

10. The method of claim 1, wherein the one or more polymorphic variations are detected at one or more positions selected from the group consisting of rs1433661, rs7679839, rs1368716, rs1905707, rs1905708, rs1994253, rs1485019, rs1905734, rs1485012, rs7670552, rs7691929, rs1948018, rs1948017, rs1485024, rs7694568, rs4693320, rs6848749, rs6532406, rs6532407 and rs6819866.

11. The method of claim 1, wherein the one or more polymorphic variations are detected in a region spanning positions 206 to 90,969 in SEQ ID NO: 3.

12. The method of claim 1, wherein the one or more polymorphic variations are detected at one or more positions selected from the group consisting of rs6886495, rs6450498, rs1472456, rs4700315, rs4700316, rs7714708, rs7710479, rs2968013, rs2968014, rs2968015, rs1391648, rs2055297, rs2055296, rs3989138, rs4700317, rs2036220, rs7727206, rs7723432, rs1546221, rs4479801, rs4395595, rs4395596, rs4699932, rs2936201, rs7356672, rs2936200, rs1909296, rs7703131, rs7445308, rs3087748, rs4321723, rs2968016, rs5868151, rs1874858, rs1874857, rs7712922, rs4631140, rs4469166, rs1078369, rs1078368, rs2968006, rs2968005, rs2936190, rs2409613, rs4415048, rs2968004, rs2968003, rs2968002, rs2936191, rs1498610, rs6874662, rs3060393, rs7729722, rs7733884, rs7714489, rs7735570, rs2936193, rs2291851, rs2291852, rs1498602, rs1995166, rs1498603, rs1498604, rs1498605, rs1948651, rs4699934, rs4700319, rs2279737, rs7720361, rs7706419, rs1006431, rs1353747, rs1498606, rs1353748, rs1553113, rs2968012, rs2968011, rs1498608, rs2936189, rs1498609, rs2968019, rs6891238, rs2968010, rs2968009, rs2936203, rs1498601, rs1498600, rs1498599, rs2936202, rs7730070, rs6450501, rs6450502, rs6889456, rs6894618, rs7706044, rs7707541, rs7712076, rs6892860, rs6867053, rs7737269, rs6864156, rs950447, rs2936196, rs7719347, rs1391649, rs1391650, rs1391651, rs1353749, rs10682149, rs5868153, rs1363882, rs2409626, rs2968018, rs954740, rs986067, rs6869400, and rs5010782.

13. The method of claim 1, wherein the one or more polymorphic variations are detected at one or more positions selected from the group consisting of rs7714708, rs1498602, rs4699934, rs1006431, rs1353747, rs1498608, rs1498609, rs2968010, rs2936202 and rs1391649.

14. The method of claim 1, wherein the one or more polymorphic variations are detected in a region spanning positions 1,599 to 82,591 in SEQ ID NO: 4.

15. The method of claim 1, wherein the one or more polymorphic variations are detected at one or more positions selected from the group consisting of rs1478398, rs1478397, rs1160114, rs1160113, rs1382323, rs1160112, rs7709870, rs7710643, rs7730467, rs6579829, rs6579830,

rs6579831, rs6896232, rs1351131, rs1038074, rs1478396, rs6880512, rs4958858, rs4958431, rs4958432, rs6898463, rs4958859, rs4130064, rs4130065, rs4133119, rs4958860, rs4958861, rs4437356, rs4958868, rs1478400, rs6889375, rs1600159, rs6875892, rs4608909, rs2345000, rs4516840, rs2054440, rs707141, rs707142, rs841236, rs707143, rs707144, rs6869405, rs707145, rs707146, rs707148, rs707150, rs5872184, rs3763015, rs2042235, rs3763013, rs2042236, rs1946234, rs1946235, rs1946236, rs8177402, rs8177403, rs8177404, rs8177405, rs8177406, rs8177407, rs8177408, rs8177409, rs6888961, rs8177410, rs8177411, rs8177412, rs8177413, rs870407, rs870406, rs6873202, rs8177414, rs8177415, rs3805435, rs8177416, rs3792799, rs3792798, rs3828599, rs8177417, rs3792797, rs8177418, rs8177419, rs8177420, rs8177421, rs4958872, rs3792796, rs8177422, rs8177423, rs4958434, rs8177424, rs8177425, rs8177426, rs8177427, rs8177429, rs6889737, rs3792795, rs8177430, rs8177431, rs4958873, rs8177432, rs8177433, rs8177434, rs8177435, rs3763011, rs8177436, rs8177437, rs4958874, rs8177439, rs8177440, rs8177441, rs8177442, rs8177443, rs869975, rs869976, rs8177444, rs8177445, rs7721469, rs8177446, rs7704191, rs8177447, rs11548, rs2230303, rs7722386, rs8177448, rs8177449, rs2070593, rs8177450, rs8177451, rs8177452, rs8177453, rs8177454, rs3763010, rs8177455, rs8177456, rs736775, rs2277940, rs8177458, rs8177834, rs3924, rs2233312, rs2233311, rs2233310, rs2233309, rs4958875, rs2233308, rs2233307, rs2233306, rs2233305, rs2233304, rs2233303, rs2233302, rs2287719, rs2287720, rs7727034, rs7727250, rs7709800, rs3840312, rs2287721, rs6875293, rs3805434, rs2080982, rs2080983, rs2287722, rs2233301, rs2233300, rs4958876, rs2233299, rs2233298, rs2287723, rs2161359, rs7734456, rs4292439, rs4958878, rs6862024, rs3834819, rs2233297, rs2233296, rs2233295, rs2233294, rs7713028, rs7713223, rs7713567, rs888989, rs2233293, rs3749657, rs2233292, rs2112635, rs871269, rs3792794, rs6579837, rs3805433, rs5872186, rs2233291, rs2233290, rs2233289, rs4958435, rs4958880, rs1422673, rs2042234, rs3805432, rs3805431, rs2233288, rs2233287, rs3815720, rs3792792, rs3792791, rs2303018, rs3792790, rs4958436, rs2233286, rs2233285, rs7732451, rs2233284, rs1422674, rs3792789, rs4562032, rs6865077, rs1559126, rs3792788, rs1559127, rs3792786, rs6880110, rs6861227, rs3805430, rs1862364, rs4958881, rs3792785, rs6869605, rs6870205, rs4246047, rs4958882, rs3792784, rs3792783 and rs5872188.

16. The method of claim 1, wherein the one or more polymorphic variations are detected at one or more positions selected from the group consisting of rs1478398, rs1160114, rs1160113, rs1160112, rs4958858, rs4958431, rs6898463, rs4958859, rs4958860, rs4608909, rs707144, rs2042235, rs3763013, rs2042236, rs8177404, rs8177426, rs8177427, rs8177429, rs3792795, rs4958873, rs8177437, rs869975, rs8177447, rs11548, rs2277940, rs8177834, rs2233311, rs2233302, rs7727034, rs7727250, rs3805434, rs7734456, rs7713028, rs7713223, rs888989, rs3792794, rs4958880, rs1422673, rs3805432 and rs4958436.

17. The method of claim 1, wherein the one or more polymorphic variations are detected in a region spanning positions 231 to 86,539 in SEQ ID NO: 5.

18. The method of claim 1, wherein the one or more polymorphic variations are detected at one or more positions in linkage disequilibrium with one or more positions in claim 3, 6, 9, 12 or 15.

19. The method of claim 1, wherein detecting the presence or absence of the one or more polymorphic variations comprises:

hybridizing an oligonucleotide to the nucleic acid sample, wherein the oligonucleotide is complementary to a nucleotide sequence in the nucleic acid and hybridizes to a region adjacent to the polymorphic variation;

extending the oligonucleotide in the presence of one or more nucleotides, yielding extension products; and

detecting the presence or absence of a polymorphic variation in the extension products.

20. The method of claim 1, wherein the subject is a human.

21. A method for identifying a polymorphic variation associated with low BMD proximal to an incident polymorphic variation associated with low BMD, which comprises:

identifying a polymorphic variation proximal to the incident polymorphic variation associated with low BMD, wherein the polymorphic variation is detected in a nucleotide sequence in SEQ ID NOs:1-5, a substantially identical sequence thereof or a fragment of the foregoing; and

determining the presence or absence of an association of the proximal polymorphic variant with low BMD.

22. The method of claim 21, wherein the incident polymorphic variation is at one or more positions in claim 3, 6, 9, 12 or 15.

23. The method of claim 21, wherein the proximal polymorphic variation is within a region between about 5 kb 5' of the incident polymorphic variation and about 5 kb 3' of the incident polymorphic variation.

24. The method of claim 21, which further comprises determining whether the proximal polymorphic variation is in linkage disequilibrium with the incident polymorphic variation.

25. The method of claim 21, which further comprises identifying a second polymorphic variation proximal to the identified proximal polymorphic variation associated with low BMD and determining if the second proximal polymorphic variation is associated with low BMD.

26. The method of claim 25, wherein the second proximal polymorphic variant is within a region between about 5 kb 5' of the incident polymorphic variation and about 5 kb 3' of the proximal polymorphic variation associated with low BMD.

27. A method for identifying a candidate molecule that increases BMD, which comprises:

(a) introducing a test molecule to a system which comprises a nucleic acid comprising a nucleotide sequence in SEQ ID NOs:1-5, a substantially identical sequence thereof or a fragment of the foregoing; or introducing a test molecule to a system which comprises a protein encoded by a nucleotide sequence in SEQ ID NOs:1-5, a substantially identical sequence thereof or a fragment of the foregoing; and

(b) determining the presence or absence of an interaction between the test molecule and the nucleic acid or protein,

whereby the presence of an interaction between the test molecule and the nucleic acid or protein identifies the test molecule as a candidate molecule that modulates BMD levels.

28. The method of claim 27, wherein the system is an animal.

29. The method of claim 27, wherein the system is a cell.

30. The method of claim 27, wherein the nucleotide sequence comprises one or more polymorphic variations associated with low BMD.

31. The method of claim 27, wherein the one or more polymorphic variations associated with low BMD are at one or more positions in claim 3, 6, 9, 12 or 15.

32. A method for treating osteoporosis in a subject, which comprises administering a candidate molecule identified by the method of claim 27 to a subject in need thereof, whereby the candidate molecule treats osteoporosis in the subject.

33. A method for identifying a candidate therapeutic for treating osteoporosis, which comprises:

(a) introducing a test molecule to a system which comprises a nucleic acid comprising a nucleotide sequence in SEQ ID NOs:1-5, a substantially identical sequence thereof or a

fragment of the foregoing; or introducing a test molecule to a system which comprises a protein encoded by a nucleotide sequence in SEQ ID NOs:1-5, a substantially identical sequence thereof or a fragment of the foregoing; and

(b) determining the presence or absence of an interaction between the test molecule and the nucleic acid or protein,

whereby the presence of an interaction between the test molecule and the nucleic acid or protein identifies the test molecule as a candidate therapeutic for treating osteoporosis.

34. A method for treating osteoporosis in a subject, which comprises contacting one or more cells of a subject in need thereof with a nucleic acid, wherein the nucleic acid comprises a nucleotide sequence in SEQ ID NOs:1-5, a substantially identical sequence thereof, a fragment of the foregoing, or a complementary nucleotide sequence of the foregoing; whereby contacting the one or more cells of the subject with the nucleic acid treats osteoporosis in the subject.

35. The method of claim 34, wherein the nucleic acid is RNA or PNA.

36. The method of claim 34, wherein the nucleic acid is duplex RNA.

37. A method for treating osteoporosis in a subject, which comprises contacting one or more cells of a subject in need thereof with a protein, wherein the protein is encoded by a nucleotide sequence which comprises a polynucleotide sequence in SEQ ID NOs:1-5, a substantially identical sequence thereof or a fragment of the foregoing; whereby contacting the one or more cells of the subject with the protein treats osteoporosis in the subject.

38. A method for treating osteoporosis in a subject, which comprises:
detecting the presence or absence of one or more polymorphic variations associated with low BMD in a nucleic acid sample from a subject, wherein the one or more polymorphic variation are detected in a nucleotide sequence in SEQ ID NOs:1-5, a substantially identical sequence thereof or a fragment of the foregoing; and administering an osteoporosis treatment to a subject in need thereof based upon the presence or absence of the one or more polymorphic variations in the nucleic acid sample.

39. The method of claim 38, wherein the one or more polymorphic variations are detected at one or more positions in claim 3, 6, 9, 12 or 15.

40. The method of claim 38, which further comprises determining BMD levels in the subject.

41. The method of claim 38, wherein the treatment is selected from the group consisting of administering bone-active phosphonates, bisphosphonates, calcitonin, estrogen, progestins, parathyroid hormone, estrogen and estrogen receptor modulators, sodium fluoride and vitamin D metabolites, a BMD level monitoring regimen, dietary counseling to promote a balanced diet rich in calcium and vitamin D, counseling to promote weight-bearing exercise and a healthy lifestyle with no smoking or excessive alcohol intake, and combinations of the foregoing.

42. A method for selecting a therapeutic treatment for treating osteoporosis in a subject, which comprises:

detecting the presence or absence of one or more polymorphic variations associated with low BMD in a nucleic acid sample from a subject, wherein the one or more polymorphic variation are detected in a nucleotide sequence in SEQ ID NOS:1-5, a substantially identical sequence thereof or a fragment of the foregoing; and

selecting and administering an osteoporosis treatment to a subject in need thereof based upon the presence or absence of the one or more polymorphic variations in the nucleic acid sample.

43. The method of claim 42, wherein the one or more polymorphic variations are detected at one or more positions in claim 3, 6, 9, 12 or 15.

44. The method of claim 42, wherein a therapeutic treatment is not selected based upon the presence of one or more polymorphic variations in the nucleic acid sample.

45. A method for detecting or preventing osteoporosis in a subject, which comprises:

detecting the presence or absence of one or more polymorphic variations associated with low BMD in a nucleic acid sample from a subject, wherein the polymorphic variation is detected in a nucleotide sequence in SEQ ID NOS:1-5, a substantially identical sequence thereof or a fragment of the foregoing; and

administering an osteoporosis treatment or detection procedure to a subject in need thereof based upon the presence or absence of the one or more polymorphic variations in the nucleic acid sample.

46. The method of claim 45, wherein the one or more polymorphic variations are detected at one or more positions in claim 3, 6, 9, 12 or 15.

47. The method of claim 45, wherein the osteoporosis treatment is selected from the group consisting of administering bone-active phosphonates, bisphosphonates, calcitonin, estrogen, progestins, parathyroid hormone, estrogen and estrogen receptor modulators, sodium fluoride and

vitamin D metabolites, a BMD level monitoring regimen, dietary counseling to promote a balanced diet rich in calcium and vitamin D, counseling to promote weight-bearing exercise and a healthy lifestyle with no smoking or excessive alcohol intake, and combinations of the foregoing.

48. A method of targeting information for preventing or treating osteoporosis to a subject in need thereof, which comprises:

detecting the presence or absence of one or more polymorphic variations associated with low BMD in a nucleic acid sample from a subject, wherein the polymorphic variation is detected in a nucleotide sequence in SEQ ID NOs:1-5, a substantially identical sequence thereof or a fragment of the foregoing; and

directing information for preventing or treating osteoporosis to a subject in need thereof based upon the presence or absence of the one or more polymorphic variations in the nucleic acid sample.

49. The method of claim 48, wherein the one or more polymorphic variations are detected at one or more positions in claim 3, 6, 9, 12 or 15.

50. The method of claim 48, wherein the information comprises a description of an osteoporosis detection procedure or treatment.

51. The method of claim 48, wherein the treatment is selected from the group consisting of administering bone-active phosphonates, bisphosphonates, calcitonin, estrogen, progestins, parathyroid hormone, estrogen and estrogen receptor modulators, sodium fluoride and vitamin D metabolites, a BMD level monitoring regimen, dietary counseling to promote a balanced diet rich in calcium and vitamin D, counseling to promote weight-bearing exercise and a healthy lifestyle with no smoking or excessive alcohol intake, and combinations of the foregoing.

52. A composition comprising a cell from a subject having low BMD or at risk of low BMD and an antibody that specifically binds to a protein, polypeptide or peptide encoded by a nucleotide sequence identical to or 90% or more identical to a nucleotide sequence in SEQ ID NOs:1-10.

53. A composition comprising a cell from a subject having low BMD or at risk of low BMD and a RNA, DNA, PNA or ribozyme molecule comprising a nucleotide sequence identical to or 90% or more identical to a portion of a nucleotide sequence in SEQ ID NOs:1-10 or nucleotide sequence complementary to the foregoing.

54. The composition of claim 53, wherein the RNA molecule is a short inhibitory RNA molecule.
55. The method of claim 37, wherein the protein is recombinant *PROL4*.